REMARKS

Applicants have carefully reviewed and considered the Office Action mailed on March 11, 2005 and the documents cited therewith.

The Examiner has withdrawn claims 30-42 from consideration pursuant to the Requirement for Restriction. Applicant has cancelled without prejudice claims 1, 3-7, 9-15, 17-24 and 50-52. As a result, claims 2, 25-49 are pending. The Examiner again has not referred to the status of claims 43-49 in the Office Action. Applicants again submit that these claims appear to be part of Group II and therefore also stand withdrawn. Clarification is requested.

Claim 2 has been amended to include the term "isolated." Support for the subject matter of claim 2 is found throughout the specification as filed. Claims 25-26 have been made independent by incorporation of some of the subject matter of claim 19. In view of these changes, the dependencies of claims 27-29 have been altered.

Applicants submit that these changes have added no new matter to the application.

Requirement for Restriction

Applicants have reviewed the Examiner's statements with regard to the restriction requirement mailed May 26, 2004, and reserve the right to file a petition and/or divisional application(s) directed to the unelected subject matter. The Examiner again has not referred to the status of claims 43-49 in the Office Action. Applicants again submit that these claims appear to be part of Group II and therefore also stand withdrawn. Clarification is requested.

§101 Rejection of the Claims

Claims 1-18 were rejected under 35 U.S.C. § 101 because the claimed invention allegedly comprises non-statutory subject matter. Applicant submits that the presently presented claims, in particular claim 2, are directed to statutory subject matter. Withdrawal of this rejection is respectfully requested.

§112, Second Paragraph, Rejection of the Claims

Claims 3-29 were rejected under 35 USC § 112, second paragraph, as allegedly indefinite. In particular, the Examiner has alleged that the language of claims 9 and 12 is

indefinite. Claims 9 and 12 has been cancelled without prejudice. The Examiner has also alleged that claim 11 is a duplicate of claim 3. Claim 11, and claims dependent therefrom, have been cancelled without prejudice. Withdrawal of this rejection is respectfully requested.

§112, First Paragraph, Rejection of the Claims

Claim 1 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Claim 1 has been cancelled without prejudice. Withdrawal of this rejection is respectfully requested.

§102 Rejection of the Claims

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Ratcliffe (WO 00/69908)

Claims 3-7, 9-15, 17-26, 28-29 and 50-52 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ratcliffe et al (WO 00/69908). According to the Examiner, Ratcliffe discloses some of the peptides of the invention, including some of the present peptides that include hydroxyproline, as evidenced by alleged known facts that reticulocyte lysate contains endogenous prolyl hydroxylase (HPHase) activity (citing page 1337 of Bruick et al., Science 294: 1337-40 (2001)) and that proline residue 564 of HIF-1α is hydroxylated by the

lysate (citing Jaakkola et al. Science 292: 468-472 (2001) at page 472). This rejection is respectfully traversed.

As indicated above, claims 3-7, 9-15, 17-24 and 50-52 have been canceled without prejudice.

Claim 25 is directed to a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a peptide that comprises an amino acid sequence SEQ ID NO:7 (YGRKKRRQRRRDLDLEMLA(Hyp)YIPMDDDFQL).

Similarly, claim 26 is directed to a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a peptide consisting essentially of amino acid sequence SEQ ID NO:4 (MLA(Hyp)TIPM).

Ratcliffe is limited to hypoxia inducible factor α peptides that do not include hydroxyproline (Hyp). The term "hydroxyproline" is not mentioned anywhere within the four corners of the Ratcliffe disclosure.

The Examiner asserts that Example N of the Ratcliffe disclosure teaches incubation of peptide SEQ ID NO:9 (PFSTQDTDLDLEMLAPYIPMDDDFQLRSFFDQLSP) with reticulocyte lysate yields a peptide with a hydroxylated proline residue at position 564. To support his allegations of such hydroxylation, the Examiner calls upon two other references (Bruick et al. Science 294: 1337-40 (2001); Jaakkola et al. Science 292: 468-72 (2001). According to the Examiner, one of skill in the art would have "inevitably" had the isolated pro-hydroxylated peptide.

Applicant submits that there is no evidence of record that Ratcliffe actually generated a peptide with a hydroxyproline. Even if some modification of the Ratcliffe SEQ ID NO:9 peptide did occur (as Racliffe concludes), Ratcliffe provides no description of what that modification might be. Ratcliffe does not identify what substance in the reticulocyte lysate might be causing in alleged peptidyl modifications. Even if *pro arguendo* we assume that a prolyl hydroxylase enzyme is present in the reticulocyte lysate, there are three proline residues in the Ratcliffe SEQ ID NO:9 peptide. Thus, even if prolyl hydroxylase were present, one of skill in the art could not know from the Ratcliffe disclosure that hydroxylation of a particular proline had occurred in the Ratcliffe SEQ ID NO:9 peptide. Similarly, one of skill in the art would not know from the

Ratcliffe disclosure whether any other peptide sequence could also be hydroxylated in the reticulocyte lysate.

Moreover, the Ratcliffe SEQ ID NO:9 peptide does not have the same sequence as the peptides in the present claims. Thus, even if one of skill in the art were somehow convinced that Ratcliffe discloses a hydroxylated peptide that peptide would not anticipate the present claims.

Applicant reminds the Examiner that an anticipation rejection under 35 U.S.C. § 102 must be based upon a single prior art reference. Use of multiple references is not permissible except (a) to show that the primary reference is enabling; (b) to explain the meaning of a term in the primary reference; or (c) to show that a characteristic not disclosed in the reference is inherent. See M.P.E.P. § 2131.01. Moreover, if the Examiner alluding to inherent anticipation in this rejection, Applicant submits that an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. Ex parte Levy, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); In re Oelrich, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Here, there can be no inherent anticipation because one of skill in the art would not necessarily conclude that the Ratcliffe peptides have exactly the same sequences and are hydroxylated at exactly the same proline as those in the present claims, even with the Bruick and Jaakkola references. Thus, use of multiple references to allege anticipation of the present hydroxyproline-containing peptides is NOT "a modest flexibility in the rule that anticipation requires that every element of the claims appear in a single reference . . . where technological facts are known to those in the field of the invention, albeit not known to judges." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991); M.P.E.P. § 2131.01(III).

Withdrawal of this rejection of claims 3-7, 9-15, 17-26, 28-29 and 50-52 is respectfully requested.

Jaakkola et al., Science 292: 468-72 (2001)

Claims 9-10 and 17-18 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Jaakkola et al. (Science 292: 468-72 (2001). Claims 9-10 and 17-18 have been cancelled without prejudice. Withdrawal of this rejection is respectfully requested.

§103 Rejection of the Claims

Claims 19-29 and 52 were rejected under 35 USC § 103(a) as allegedly unpatentable over Jaakkola et al. (Science 292: 468-72 (2001) taken with U.S. Patent 6,124,131 to Semenza. The Examiner has stated that Jaakkola et al. discloses Applicant's SEQ ID NO:5 and that Semenza discloses a peptide with the sequence: DLDLEMLAPYIPMID.

This rejection is respectfully traversed. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed combination. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (MPEP § 2143). The teaching or suggestion to arrive at the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (MPEP § 2143, citing with favor *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Claim 25 is directed to a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a peptide that comprises amino acid sequence SEQ ID NO:7 (YGRKKRRQRRRDLDLEMLA(Hyp)YIPMDDDFQL).

Similarly, claim 26 is directed to a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a peptide consisting essentially of amino acid sequence SEQ ID NO:4 (MLA(Hyp)TIPM).

First, the combination of Jaakkola et al. and Semenza et al. does not teach or suggest all the claim elements. In particular, the combination does not disclose Applicants' SEQ ID NO:7 and SEQ ID NO:4.

Second, there is no motivation to arrive at Applicants' invention from the combination of Jaakkola et al. and Semenza et al. because Jaakkola et al. teach that even a single amino acid

change in the peptide reduces peptide interaction with VHL (see Jaakkola ate 471-70 and Fig.3. Hence, one of skill in the art would not be motivated to alter the peptide sequences of Jaakkola et al. and Semenza et al. without guidance or indication that the amino changes would improve peptide activity (rather than abrogate peptide activity).

Finally, there is no expectation of success. The combination of documents cited by the Examiner is merely an invitation to experiment. Given that some amino acid changes abrogate peptide activity, even if Jaakkola and/or Semenza were to provide data indicating that some amino acid changes improve such activity, one of skill in the art would not expect to successfully produce Applicant's invention from the Jaakkola et al. and Semenza et al. disclosures alone. No guidance to arrive at Applicants' invention exists, except Applicants' own disclosure. Withdrawal of this rejection is respectfully requested.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date June 13, 2005 By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 13 day of June 2005.

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